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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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Date of mailing (day/month/year) 28 June 2000 (28.06.00)	
International application No. PCT/EP99/08702	**Applicant's or agent's file reference** DIR 0560
International filing date (day/month/year) 10 November 1999 (10.11.99)	**Priority date** (day/month/year) 13 November 1998 (13.11.98)
Applicant FEENSTRA, Roelof, W. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 263/58, 413/04, A61K 31/42, C07D 209/34, 401/04, 277/68, 417/04, 235/26, A61K 31/425, 31/4164, 31/40, A61P 25/00

A1

(11) International Publication Number: WO 00/29397

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/EP99/08702

(22) International Filing Date: 10 November 1999 (10.11.99)

(30) Priority Data:
98203871.3 13 November 1998 (13.11.98) EP

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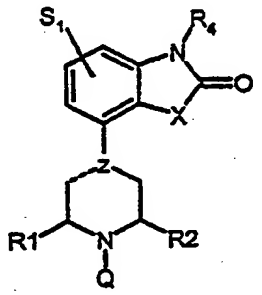
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW PIPERAZINE AND PIPERIDINE COMPOUNDS

(57) Abstract

The invention relates to a group of novel piperazine and piperidine derivatives of formula (I), wherein: S_1 is hydrogen, halogen, alkyl (1–3C), CN, CF_3, OCF_3, SCF_3, alkoxy (1–3C), amino or mono– or di-alkyl (1–3C) substituted amino, or hydroxy; X represents NR_3, S, CH_2, O, SO or SO_2, wherein R_3 is H or alkyl (1–3C);.....Z represents =C or –N; – R_1 and R_2 independently represent H or alkyl (1–3C), or R_1 and R_2 together can form a bridge of 2 or 3 C–atoms; R_4 is hydrogen or alkyl (1–3C); Q is methyl, ethyl, ethyl substituted with one or more fluorine atoms, cyclopropyl – methyl, optionally substituted with one or more fluorine atoms, and salts and prodrugs thereof. It has been found that these compounds have both partial dopamine D_2–receptor agonism and partial serotonin 5–HT_{1A}–receptor agonism mediated activities.



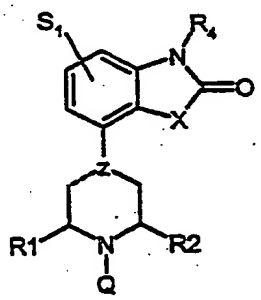
(I)

New piperazine and piperidine compounds

The present invention relates to a new group of piperazine and di-dehydropiperidine derivatives having interesting pharmacological properties due to a combination of both partial dopamine D_2-receptor agonism and partial serotonin 5-HT_{1A}-receptor agonism mediated activities. In addition, affinity for adrenergic α_1-receptors is present.

It is known from EP 0189612 that piperazine derivatives substituted at one nitrogen with a phenyl-heterocyclic group, and unsubstituted at the other nitrogen atom, have psychotropic activity.
Further it is known from EP 0190472 that benzofuran- and benzodioxole-piperazine derivatives substituted at the other nitrogen atom of the piperazine group, have also psychotropic activity.
Finally it is known from EP 0169148 that 1,3-dihydro-4-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-2H-indol-2-one and similar compounds have analgetic properties.

It has now surprisingly been found that a small group of piperazine and piperidine derivatives having formula (I)



(I)

wherein
- S_1 is hydrogen, halogen, alkyl (1-3C), CN, CF_3, OCF_3, SCF_3, alkoxy (1-3C), amino or mono- or dialkyl (1-3C) substituted amino, or hydroxy,
- X represents NR_3, S, CH_2 , O, SO or SO_2, wherein R_3 is H or alkyl (1-3C),
- .....Z represents =C or -N,
- R_1 and R_2 independently represent H or alkyl (1-3C), or R_1 and R_2 together can form a bridge of 2 or 3 C-atoms,
- R_4 is hydrogen or alkyl (1-3C),

- Q is methyl, ethyl, ethyl substited with one or more fluorine atoms, cyclopropyl - methyl, optionally substituted with one or more fluorine atoms,
with the proviso that when S_1, R_1, R_2 and R_4 are hydrogen, ...Z is =C and Q is ethyl, X cannot represent CH_2,
and salts and prodrugs thereof have a combination of partial dopamine D_2-receptor agonism and partial serotonin 5-HT_{1A}-receptor agonism activities.

Preferred compounds according to the invention are compounds of the formula (I) wherein S_1, R_1, R_2 and R_4 are hydrogen, X represents oxygen, and .....Z and Q have the above meanings, and the salts thereof.
Especially preferred are the compounds wherein S_1, R_1, R_2 and R_4 are hydrogen, X is oxygen, ...Z represents -N and Q is methyl or ethyl and salts thereof. The most preferred compound being the one wherein Q is methyl.

Compounds according to the invention show affinities for both the dopamine D_2 receptor (pKi range 7.5 – 8.5) and the serotonin 5-HT_{1A} receptor (pKi range 7.0 - 8.0) measured according to well-defined methods (e.g.: Creese I, Schneider R and Snyder SH, [^{3}H]-Spiroperidol labels dopamine receptors in rat pituitary and brain, *Eur J Pharmacol* 1997, **46**: 377-381 and Gozlan H, El Mestikawy S, Pichat L, Glowinsky J and Hamon M, 1983, Identification of presynaptic serotonin autoreceptors using a new ligand ^{3}H-PAT, *Nature* 1983, **305**: 140-142).

The compounds show varying activities as partial agonists at the dopamine D_2 receptor and, surprisingly, at the 5-HT_{1A} receptor. This activity was measured on the formation of adenylate cyclase in cell-lines expressing these cloned receptors (e.g. human D_2 receptors and 5-HT_{1A} receptors expressed in CHO cell line according to the methods described by Solomon Y, Landos C, Rodbell M, 1974, A highly selective adenylyl cyclase assay, *Anal Biochem* 1974, **58**: 541-548 and Weiss S, Sebben M and Bockaert JJ, 1985, Corticotropin-peptide regulation of intracellular cyclic AMP production in cortical neurons in primary culture, *J Neurochem* 1985, **45**:869-874).

The unique combination of both partial dopamine D_2 -receptor agonism and partial serotonin 5-HT_{1A} -receptor agonism results in a surprisingly broad activity in several animal models, predictive for psychiatric and/or neurologic disturbances.
The compounds show a surprisingly high efficacy in a therapeutic model for anxiolytic/antidepressant activity: the conditioned ultrasonic vocalization model in rats (see e.g.: Molewijk HE, Van der Poel AM, Mos J, Van der Heyden JAM and Olivi r B

(1995), Conditioned ultrasonic vocalizations in adult male rats as a paradigm for screening anti-panic drugs, *Psychopharmacology* 1995,117: 32-40). The activity of the compounds in this model was in the low microgram/kg range, which is surprisingly more active (by a factor 100 to 3000) compared to the compounds previously described in EP 0190472 and EP 0398413.

In addition these compounds also show effects in models predictive for antidepressant activity at higher doses (forced swim test, see e.g.: Porsolt RD, Anton G, Blavet N and Jalfre M, 1978, Behavioural despair in rats: A new model sensitive to antidepressant treatments, *Eur J Pharmacol* 1978, 47:379-391 and the differential reinforcement of low rates of responding model in rats, see e.g.: McGuire PS and Seiden LS, The effects of tricyclic antidepressants on performance under a differential-reinforcement-of-low-rate schedule in rats, *J Pharmacol Exp Ther* 1980, 214: 635-641).

At higher doses also dopamine antagonist-like effects were observed (antagonism of apomorphine-induced climbing behaviour in mice, (A), e.g.: Costall B, Naylor RJ and Nohria V, Differential actions of typical and atypical agents on two behavioural effects of apomorphine in the mouse, (B), *Brit J Pharmacol* 1978, 63: 381-382; suppression of locomotor activity, e.g.: File SE and Hyde JRG, A test of anxiety that distinguishes between the actions of benzodiazepines and those of other minor tranquillisers or stimulants, *Pharmacol Biochem Behav* 1979, 11: 65-79 and inhibition of conditioned avoidance response in rats, e.g.: Van der Heyden JAM, Bradford LD, A rapidly acquired one-way conditioned avoidance procedure in rats as a primary screening test for antipsychotics: influence of shock intensity on avoidance performance, *Behav Brain Res* 1988, 31: 61-67). The first two activities, A and B, have previously been reported for partial dopamine D_2 -receptor agonists by Mewshaw et.al, *Bioorg. Med. Chem. Lett.* 8 (1998) 2675.

The compounds are likely to be of value in the treatment of affections or diseases of the central nervous system, caused by disturbances of the dopaminergic and/or serotonergic systems, for example: anxiety disorders (including e.g. generalised anxiety. Panic, Obsessive compulsive disorder), depression, autism, schizophrenia, Parkinson's disease, disturbances of cognition and memory.

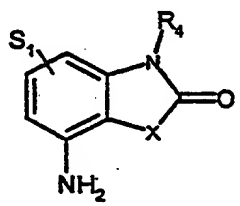
Suitable acids with which the compounds of the invention can form acceptable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric

acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and naphtalene sulphonic acid.

Prodrugs are derivatives of the compounds having formula (I) wherein R_4 is a group which is easily removed after administration. Suitable prodrugs for example are compounds wherein N-R_4 is one of the following groups: amidine, enamine, a Mannich base, a hydroxy-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate or enaminone.

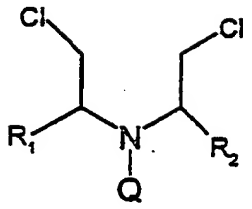
The compounds and the salts thereof can be brought into forms for administration by means of usual processes using auxiliary substances such as liquid and solid carrier materials.

The compounds of the invention can be prepared according to methods known for the synthesis of analogous compounds.
Compounds having formula (I) can be obtained by reacting the corresponding compound wherein Q is hydrogen with a compound Q-Hal, wherein Q is methyl (optionally fluorinated) ethyl, or (optionally fluorinated) cyclopropylmethyl and Hal is halogen, preferably iodine. This reaction can be carried out in a solvent such as acetonitrile in the presence of a base, for example ethyl-diisopropylamine or triethylamine.
The starting compounds wherein Q is hydrogen and ...Z is -N are known or can be obtained as described in EP 0189612. Starting compounds wherein Q is hydrogen and ...Z is $=CH_2$ can be obtained as described below.
The compounds of the invention wherein ...Z is -N, can also be obtained by reacting a compound having formula (II)



(II)

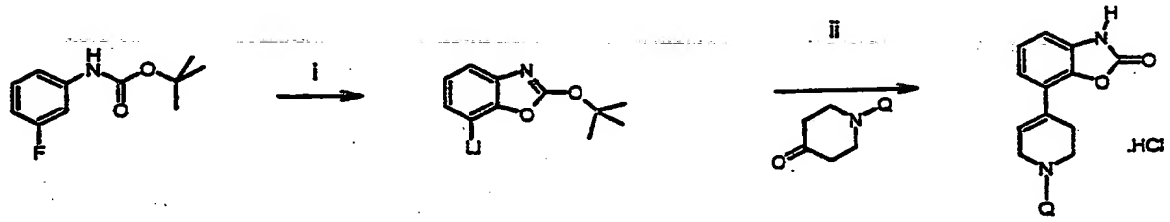
with a compound of the formula (III)



(III)

in which formulae the symbols have the above meanings. This reaction can be carried out in an organic solvent such as chlorobenzene.

The compounds having formula (I) wherein .....Z represents =C can also be obtained according to the method indicated in the following scheme:



The starting compound for step (i) can be obtained according to the procedure described in J. Org. Chem. 45, (1980), 4789, and step (i) itself can be carried out as described in J. Org. Chem., 47, (1982), 2804.

Step (ii) is carried out in a manner known for this type of chemical reactions, and is elucidated in Example 3.

The invention will be illustrated in the following Examples:

Example 1:

1.28 g (5 mmol) of I-H.HCl was suspended in 25 ml of acetonitrile and 0.34 ml (4.4 mmol) of ethyliodide together with 5 ml of di-isopropyl ethyl amine were added. The resulting reaction mixture was stirred and refluxed for 18 hrs under a nitrogen atmosphere. The reaction mixture was allowed to reach room temperature after which a small quantity of SiO_2 was added. The resulting suspension was concentrated *in vacuo*

leaving a powder which was put on top of a chromatography column after which a chromatography run was done (SiO_2 , eluent CH_2Cl_2/MeOH 95/5) yielding 0.55 g of a white solid. The latter was crystallized from EtOAc/EtOH (ca. 1/1) to which 1.1 equivalent of 1 M HCl/EtOH was added. The crystals were collected by filtration, washing with respectively EtOAc and di-ethyl ether yielded after drying 0.5 g (42%) of the desired HCl salt of the compound wherein S_1, R_1, R_2 and R_4 are hydrogen, X is oxygen, ...Z is -N, and Q is ethyl, mp 280-2 °C (dec.).

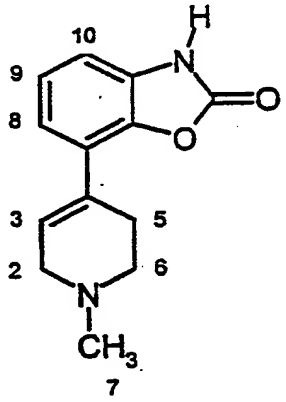
Example 2:

6.0 g (40 mmol) of the compound having formula (II) (wherein S_1 and R_4 are hydrogen and X is oxygen) was dissolved in 150 ml of chlorobenzene after which 8.47 g (44 mmol) of N-methyl-bis(chloro-ethyl)amine monohydrochloride was added. The resulting reaction mixture was stirred and brought to reflux. The water present in the starting materials was separated by means of a Dean-Stark device. After 44 hrs solid material had formed and the reaction mixture was allowed to reach room temperature. The liquid was separated, the residue was washed with toluene after which it was refluxed in ethanol. After cooling the solid material was filtered and subsequently purified by flash column chromatography (SiO_2, eluent: CH_2Cl_2/MeOH/NH_4OH = 97/2.5/0.5). This procedure yielded 4.5 g of solid material which was dissolved in 96% EtOH (ca. 300 ml) after which, while stirring, 2 equivalents of 1M HCl/MeOH were added. Crystallization started and eventually, after filtration and drying, 4.15 g (38%) of the hydrochloride of the desired compound wherein S_1, R_1, R_2 and R4 are hydrogen, X is oxygen, ...Z is -N, and Q is methyl could be isolated, mp 301.5-302.5 °C.

Example 3:

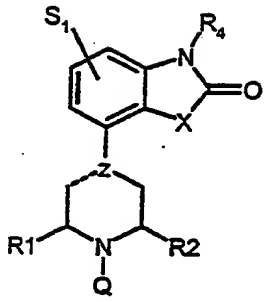
Under an inert atmosphere, 16.5 g (78.2 mmol) of N-(*tert.*butyloxycarbonyl)-*meta*-fluoroaniline were dissolved in 230 ml of dry tetrahydrofuran (THF) after which the solution was cooled to –75 °C (dry ice , acetone). While stirring a commercially available solution of 1.5 M *tert.*butyl-lithium in heptane (ca. 156 mmol, 2 molequivalents) was added slowly, after which the reaction mixture was stirred for 0.5 hr at –70 °C, and subsequently for an additional 2 hrs at –25 °C. Again the reaction mixture was brought to –75 °C and a solution of 9.6 ml of N-methylpiperidone (78.2 mmol, 1 molequivalent) in ca. 25 ml of dry THF. The reaction mixture was allowed to reach room temperature and stirred for an additional 16 hrs. Subsequently a solution of 1.5 ml (83 mmol) of H_2O in 50 ml of MeOH was added slowly to the reaction mixture, after which 100 ml of SiO_2 was added. The suspension was evaporated to dryness after which the resulting powdery residu was put on top of a chromatography column

after which a "flash"-chromatography run was done (SiO_2 , first eluent: EtOAc, second eluent: MeOH/EtOAc/tri-ethylamine 15/85/1) yielding 12.4 g of a dark yellow oil.
While stirring, 4.7 g (ca. 15.5 mmol) of the obtained product were dissolved in 100 ml of dioxan after which 100 ml of concentrated HCl was added, the resulting mixture was refluxed for 1 hr. The reaction mixture was allowed to reach room temperature after which it was concentrated *in vacuo*, yielding a solid residu. The residu was suspended and stirred in *i*-propanol after which the solid material was filtered and subsequently washed with respectively EtOAc, di-ethyl ether and hexane. After drying 3.1 g of residu was left of which 1.5 g was suspended in EtOH, the latter suspension being refluxed for 1 hr. The mixture was allowed to reach room temperature after which it was filtered, yielding a residu which was washed with absolute EtOH and di(*i*-propyl) ether respectively. After drying 1.1 g (53%) of the desired compound wherein S_1, R_1, R_2 and R_4 are hydrogen, X is oxygen, ...Z is =C, and Q is methyl was obtained, ^{1}H-NMR(400 MHz, D_2O) :
^{1}H-NMR(400 MHz, D_2O): δ 2.96 (broad, 2H, H-5); 3.04 (s, 3H, H-7); 3.3-4.3 (broad, 4H, H-2, H-6); 6.4 (m, 1H, H-3); 7.14 (d, 1H, H-8 or H-10, J=8 Hz); 7.2 (d, 1H, H-10 or H-8, J=8 Hz); 7.26 (t, 1H, H-9, J=8 Hz), using the numbering as indicated in the following formula:



Claims

1. Compounds having formula (I)



(I)

wherein

- S_1 is hydrogen, halogen, alkyl (1-3C), CN, CF_3, OCF3, SCF3, alkoxy (1-3C), amino or mono- or dialkyl (1-3C) substituted amino, or hydroxy,
- X represents NR_3, S, CH_2 or O, SO or SO_2, wherein R_3 is H or alkyl (1-3C),
- ...Z represents =C or -N,
- R_1 and R_2 independently represent H or alkyl (1-3C), or R_1 and R_2 together can form a bridge of 2 or 3 C-atoms,
- R_4 is hydrogen or alkyl (1-3C),
- Q is methyl, ethyl, ethyl substituted with one or more fluorine atoms, or cyclopropylmethyl optionally substituted with one or more fluorine atoms,

with the proviso that when S_1, R_1, R_2 and R_4 are hydrogen, ...Z is =C and Q is ethyl, X cannot represent CH_2,

and salts and prodrugs thereof.

2. Compounds as claimed in claim 1, wherein S_1, R_1, R_2 and R_4 are hydrogen, X represents oxygen, Q is methyl or ethyl and ...Z has the meaning given in claim 1.

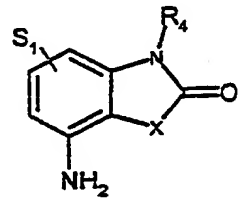
3. Compounds as claimed in claim 2, wherein .....Z represents -N.

4. A compound as claimed in claim 3 wherein Q is methyl.

5. Method for the preparation of the compounds claimed in claim 1 by reacting a compound having formula (I) wherein Q is hydrogen, with a compound of the formula

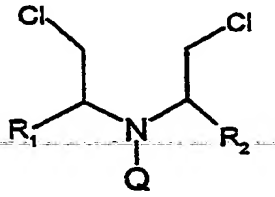
Q-Hal wherein Q is methyl or (optionally fluorinated) ethyl, (optionally fluorinated) cyclopropylmethyl and Hal is halogen.

6. Method for the preperation of compounds as claimed in claim 1 wherein ...Z represents -N by reacting a compound having formula (II).



(II)

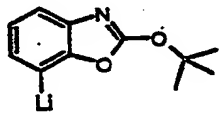
with a compound having formula (III)



(III)

in which formulae the symbols have the meanings given in claim 1.

7. Method for the preparation of compounds having formula (I) wherein .....Z represents =C, by reacting a compound having formula (IV)



(IV)

with a piperidone derivative which is optionally R_1 and/or R_2 substituted, and carries a group Q, followed by dehydration and deprotection.

8. Pharmaceutical compositions which contain at least one compound as claimed in claim 1 as an active component.

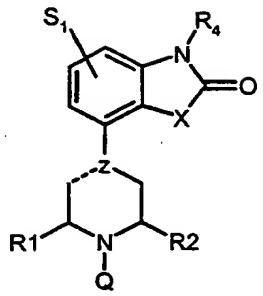
9. Method of preparing a pharmaceutical composition, characterized in that a compound as claimed in claim 1 is brought into a form suitable for administration.

10. A method of treating CNS disorders, characterized in that a compound as claimed in claim 1 is used.

11. A method of treating anxiety and/or depression, characterized in that a compound as claimed in claim 1 is used.

Claims

1. Compounds having formula (I)



(I)

wherein

- S_1 is hydrogen, halogen, alkyl (1-3C), CN, CF_3, OCF3, SCF3, alkoxy (1-3C), amino or mono- or dialkyl (1-3C) substituted amino, or hydroxy,
- X represents NR_3, S, CH_2 or O, SO or SO_2, wherein R_3 is H or alkyl (1-3C),
- ...Z represents =C or -N,
- R_1 and R_2 independently represent H or alkyl (1-3C), or R_1 and R_2 together can form a bridge of 2 or 3 C-atoms,
- R_4 is hydrogen or alkyl (1-3C),
- Q is methyl, ethyl, ethyl substituted with one or more fluorine atoms, or cyclopropylmethyl optionally substituted with one or more fluorine atoms,

with the proviso that when S_1, R_1, R_2 and R_4 are hydrogen, ...Z is =C and Q is ethyl, X cannot represent CH_2,

and salts and prodrugs thereof.

2. Compounds as claimed in claim 1, wherein S_1, R_1, R_2 and R_4 are hydrogen, X represents oxygen, Q is methyl or ethyl and ...Z has the meaning given in claim 1.

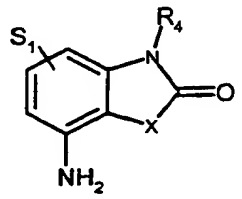
3. Compounds as claimed in claim 2, wherein .....Z represents -N.

4. A compound as claimed in claim 3 wherein Q is methyl.

5. Method for the preparation of the compounds claimed in claim 1 by reacting a compound having formula (I) wherein Q is hydrogen, with a compound of the formula

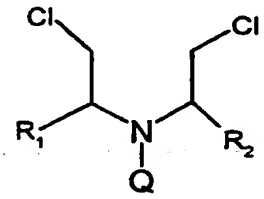
Q-Hal wherein Q is methyl or (optionally fluorinated) ethyl, (optionally fluorinated) cyclopropylmethyl and Hal is halogen.

6. Method for the preperation of compounds as claimed in claim 1 wherein ...Z represents -N by reacting a compound having formula (II).



(II)

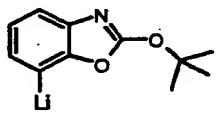
with a compound having formula (III)



(III)

in which formulae the symbols have the meanings given in claim 1.

7. Method for the preparation of compounds having formula (I) wherein .....Z represents =C, by reacting a compound having formula (IV)



(IV)

with a piperidone derivative which is optionally R_1 and/or R_2 substituted, and carries a group Q, followed by dehydration and deprotection.

8. Pharmaceutical compositions which contain at least one compound as claimed in claim 1 as an active component.

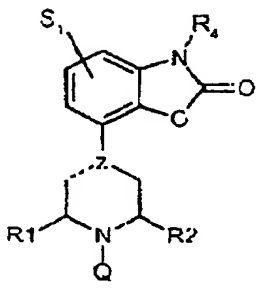
9. Method of preparing a pharmaceutical composition, characterized in that a compound as claimed in claim 1 is brought into a form suitable for administration.

10. A method of treating CNS disorders, characterized in that a compound as claimed in claim 1 is used.

11. A method of treating anxiety and/or depression, characterized in that a compound as claimed in claim 1 is used.

Claims

1. Compounds having formula (I)



(I)

wherein

- S_1 is hydrogen, halogen, alkyl (1-3C), CN, CF_3, OCF3, SCF3, alkoxy (1-3C), amino or mono- or dialkyl (1-3C) substituted amino, or hydroxy,
- ...Z represents =C or -N,
- R_1 and R_2 independently represent H or alkyl (1-3C), or R_1 and R_2 together can form a bridge of 2 or 3 C-atoms,
- R_4 is hydrogen or alkyl (1-3C),
- Q is methyl, ethyl, ethyl substituted with one or more fluorine atoms, or cyclopropylmethyl optionally substituted with one or more fluorine atoms,

and salts and prodrugs thereof.

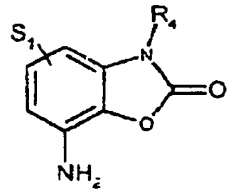
2. Compounds as claimed in claim 1, wherein S_1, R_1, R_2 and R_4 are hydrogen, Q is methyl or ethyl and ...Z has the meaning given in claim 1.

3. Compounds as claimed in claim 2, wherein .....Z represents -N.

4. A compound as claimed in claim 3 wherein Q is methyl.

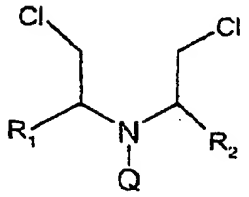
5. Method for the preparation of the compounds claimed in claim 1 by reacting a compound having formula (I) wherein Q is hydrogen, with a compound of the formula Q-Hal wherein Q is methyl or (optionally fluorinated) ethyl, (optionally fluorinated) cyclopropylmethyl and Hal is halogen.

6. Method for the preperation of compounds as claimed in claim 1 wherein ...Z represents -N by reacting a compound having formula (II).



(II)

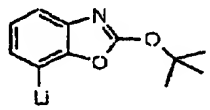
with a compound having formula (III)



(III)

in which formulae the symbols have the meanings given in claim 1.

7. Method for the preparation of compounds having formula (I) wherein .....Z represents =C, by reacting a compound having formula (IV)



(IV)

with a piperidone derivative which is optionally R_1 and/or R_2 substituted, and carries a group Q, followed by dehydration and deprotection.

8. Pharmaceutical compositions which contain at least one compound as claimed in claim 1 as an active component.

9. Method of preparing a pharmaceutical composition, characterized in that a compound as claimed in claim 1 is brought into a form suitable for administration.

10. A method of treating CNS disorders, characterized in that a compound as claimed in claim 1 is used.

11. A method of treating anxiety and/or depression, characterized in that a compound as claimed in claim 1 is used.

TENT COOPERATION TR Y

REC'D 26 JAN 2001

WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DIR 0560		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/08702	10/11/1999	13/11/1998
International Patent Classification (IPC) or national classification and IPC C07D263/58		
Applicant DUPHAR INTERNATIONAL RESEARCH BV et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/05/2000	24.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Usuelli, A Telephone No. +49 89 2399 7366

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08702

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-11 with telefax of 09/01/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 10,11.

because:

   ☒ the said international application, or the said claims Nos. 10,11 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-9

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

For the assessment of the present claims 10-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

1- Reference is made to the following documents:

D(1) = WO-A-9736893
D(2) = EP-A-169148
D(3) = EP-A-189612
D(4) = EP-A-190472
D(5) = WO-A-9413659
D(6) = WO-A-9603400
D(7) = EP-A-900792

1- Novelty
The compounds of the present application differ from the compounds of D(2) and D(6) in that they contain a benzooxazole instead of the indole ring.
The compounds disclosed in documents D(1), D(3), D(5) differ from the compounds of the invention in that they have different substituents on the tetrahydropyridine/piperazine ring.
The general formula (I) of D(4) overlaps with the general formula (I) of the present application, but the specific compounds disclosed in the document are not closely related to the compounds of the invention and the overlapping area is therefore considered novel.

2- Inventive step
2.1- D(1) discloses piperidine and piperazine derivatives suitable for the treatment of

psychotic disorders and having affinity for the D_2 and 5-HT_{1a} receptors. D(3) and D(4) relate to piperazine derivatives which can be used for the treatment of CNS diseases like psychosis and depression. Due to the similarity of the compounds of D(3) to the compounds of the invention having a piperazine ring (Z: -N), D(3) is regarded as the closest prior art for this class of compounds. For the class of compounds of formula (I) having a tetrahydropyridine ring (Z: =C) D(1), which discloses piperazine and piperidine derivatives, represents the closest prior art.

2.2- The compounds of D(3) differ from the compounds of the invention having a piperazine ring (Z: -N) only in that the piperazine ring is substituted by a hydrogen instead of a methyl, ethyl or a cyclopropyl group. However, the Applicant has shown by means of a comparative test that the substitution on the nitrogen atom of the piperazine ring is of great importance for the activity. In particular, in a therapeutic model for anxiolytic/antidepressant activity, the compound of the example 2 of the invention having a methyl group on the free nitrogen atom of the piperazine ring was found more than 600 times as active as the corresponding compound of D(3) having a hydrogen in the same position.

2.3- For the compounds of the invention having a tetrahydropyridine ring (Z: =C), D(1) is considered as the closest prior art. The compounds of D(1) differ from the compounds of the invention in that the tetrahydropyridine/piperazine ring is substituted by an aryl or heteroaryl/benzyl group. There are no suggestions in the prior art documents which would have led the skilled person to modify the compounds of D(1) in the opportune way in order to arrive at the compounds of the invention.

2.4- In view of these considerations, an inventive step can be acknowledged for the compounds of formula (I) for which the claimed activity has been credibly shown.
However, in order to acknowledge an inventive step for the whole class of the compounds claimed, the property establishing an inventive step must extend to all these compounds. The Applicant has submitted experimental tests which demonstrate the activity of some molecules. However, the non-limitative definition "prodrug" used in the claims has the effect to extend the scope of the present claims to a broad and unlimited class of compounds. For instance, prodrugs of the compounds of formula (I) could be obtained attaching various groups (cf. page 4) to at least two different positions of the molecules. It appears that there is no basis for assuming that the activity shown for some specific

compounds can be generalized to all the possible compounds encompassed by the functional definition "prodrug". Accordingly, it cannot be assumed that all the claimed compounds indeed represent a solution of the technical problem.
Therefore, claims 1-11 do not fulfil the requirements of Art. 33(3) PCT.

3- Industrial applicability
Claims 10-11 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
98202832.6 EP-A-900792	10.03.1999	24.08.1998	02.09.1997

The priority documents pertaining to the present application were not available at the time of establishing this first written opinion. Hence, it is based on the assumption that all the claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-document cited in the international search report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

Re Item VII
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D(1) is not mentioned in the description, nor is this document identified therein.

ENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
DIR 0560		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 08702	10/11/1999	13/11/1998
Applicant		
DUPHAR INTERNATIONAL RESEARCH BV et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rul 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by th applicant.

[ ] None of th figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes th invention.

INTERNATIONAL SEARCH REPORT

[redacted]national application N .
PCT/EP 99/ 08702

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 10-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by th applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/08702

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/58 C07D413/04 A61K31/42 C07D209/34 C07D401/04
C07D277/68 C07D417/04 C07D235/26 A61K31/425 A61K31/4164
A61K31/40 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 36893 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 9 October 1997 (1997-10-09) claims	1-11
Y	EP 0 169 148 A (ROUSSEL UCLAF) 22 January 1986 (1986-01-22) cited in the application claims	1-11
A	EP 0 189 612 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 6 August 1986 (1986-08-06) cited in the application claims	1-11
A	EP 0 190 472 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 13 August 1986 (1986-08-13) cited in the application claims	1-11

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2000	21/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]EP 99/08702

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 13659 A (H. LUNDBECK & CO AS) 23 June 1994 (1994-06-23) claims	1-11
A	WO 96 03400 A (PFIZER INC) 8 February 1996 (1996-02-08) claims	1-11
P,X	EP 0 900 792 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 10 March 1999 (1999-03-10) claims	1-11

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]P 99/08702

Patent document cited in search report		Publication dat	Patent family member(s)		Publication date
WO 9736893	A	09-10-1997	AU	708053 B	29-07-1999
			AU	2029497 A	22-10-1997
			CA	2250347 A	09-10-1997
			CN	1215400 A	28-04-1999
			CZ	9803068 A	13-01-1999
			EP	0889889 A	13-01-1999
			NO	984533 A	02-11-1998
			PL	329123 A	15-03-1999
			SK	133198 A	11-02-1999
EP 0169148	A	22-01-1986	FR	2567884 A	24-01-1986
			JP	6057706 B	03-08-1994
			JP	61037780 A	22-02-1986
			US	4737505 A	12-04-1988
EP 0189612	A	06-08-1986	AT	81975 T	15-11-1992
			AU	588015 B	07-09-1989
			AU	5139185 A	26-06-1986
			CA	1271475 A	10-07-1990
			DE	3586794 A	10-12-1992
			DK	586085 A	22-06-1986
			ES	550104 A	16-12-1986
			GR	853064 A	09-04-1986
			IE	61723 B	30-11-1994
			IL	77395 A	16-08-1991
			JP	61152655 A	11-07-1986
			NZ	214610 A	29-09-1988
			PH	24503 A	18-07-1990
			US	5424313 A	13-06-1995
EP 0190472	A	13-08-1986	AT	44528 T	15-07-1989
			AU	589387 B	12-10-1989
			AU	5139085 A	17-07-1986
			AU	5139285 A	26-06-1986
			DK	589985 A	22-06-1986
			DK	590085 A	22-06-1986
			EP	0185429 A	25-06-1986
			ES	550106 A	01-04-1987
			ES	557359 A	16-07-1988
			GR	853063 A	09-04-1986
			GR	853065 A	09-04-1986
			IE	58916 B	01-12-1993
			IL	77396 A	09-02-1990
			JP	61152662 A	11-07-1986
			JP	61152666 A	11-07-1986
			NZ	214611 A	30-06-1988
			NZ	214612 A	30-06-1988
			PH	23958 A	23-01-1990
			PH	22040 A	13-05-1988
			US	4782061 A	01-11-1988
			ZA	8509662 A	27-08-1986
			ZA	8509664 A	27-08-1986
WO 9413659	A	23-06-1994	AT	176909 T	15-03-1999
			AU	675263 B	30-01-1997
			AU	5561894 A	04-07-1994
			CA	2151378 A	23-06-1994
			CZ	9501517 A	17-01-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]P 99/08702

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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